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A Randomized Trial of Isonitrogenous Enteral Diets After Severe Trauma

An Immune-Enhancing Diet Reduces Septic Complications

Kenneth A. Kudsk, M.D.,* Gayle Minard, M.D.,* Martin A. Croce, M.D.,* Rex O. Brown, Pharm.D.,† Trudy S. Lowrey, R.D.,‡, F. Elizabeth Pritchard, M.D.,* Roland N. Dickerson, Pharm.D.,† and Timothy C. Fabian, M.D.*

From the Departments of Surgery and Clinical Pharmacy,† The University of Tennessee, Memphis, and the Department of Food and Nutrition Services,‡ The Regional Medical Center at Memphis, Memphis, Tennessee*

Objective

The authors randomized patients to an enteral diet containing glutamine, arginine, omega-3 fatty acids, and nucleotides or to an isonitrogenous, isocaloric diet to investigate the effect of septic outcome. A third group of patients, without enteral access but eligible by severity of injury, served as unfed controls and were studied prospectively to determine the risk of infection.

Summary Background Data

Laboratory and clinical studies suggest that diets containing specialty nutrients, such as arginine, glutamine, nucleotides, and omega-3 fatty acids, reduce septic complications. Unfortunately, most clinical trials have not compared these diets *versus* isonitrogenous, isocaloric controls. This prospective, blinded study randomized 35 severely injured patients with an Abdominal Trauma Index ≥ 25 or a Injury Severity Score ≥ 21 who had early enteral access to an immune-enhancing diet ([IED] Immun-Aid, McGaw, Inc., Irvine, CA; n = 17) or an isonitrogenous, isocaloric diet (Promote [Ross Laboratories, Columbus, OH] and Casec [Mead-Johnson Nutritionals, Evansville, IN]; n = 18) diet. Patients without early enteral access but eligible by severity of injury served as contemporaneous controls (n = 19). Patients were evaluated for septic complications, antibiotic usage, hospital and intensive care unit (ICU) stay, and hospital costs.

Results

Two patients died in the treatment group and were dropped from the study. Significantly fewer major infectious complications (6%) developed in patients randomized to the IED than patients in the isonitrogenous group (41%, p = 0.02) or the control group (58%, p = 0.002). Hospital stay, therapeutic antibiotics, and the development of intra-abdominal abscess was significantly lower in patients receiving the IED than the other two groups. This improved clinical outcome was reflected in reduced hospital costs.

Conclusions

An IED significantly reduces major infectious complications in severely injured patients compared with those receiving isonitrogenous diet or no early enteral nutrition. An IED is the preferred diet for early enteral feeding after severe blunt and penetrating trauma in patients at risk of subsequent septic complications. Unfed patients have the highest complication rate.

Although the responsible mechanisms are unknown, delivery of specialized nutrition support via the gastrointestinal tract rather than intravenously reduces septic morbidity in severely injured trauma patients.[1-4] Improved mucosal immunity,[5,6] normal gut-barrier function,[7-9] and improved nutritional status all have been implicated in this improved clinical outcome. Accumulating experimental and clinical evidence suggests that enteral feeding supplemented with specific nutrients, such as glutamine, arginine, omega-3 polyunsaturated fatty acids, or nucleotides, further improves clinical outcome. Several clinical studies show reduced hospital stay or reduced septic complications in patients randomized to these supplemented immune-enhancing diets (IEDs).[10-16] Patients undergoing surgery for upper gastrointestinal malignancies who received a diet enriched in omega-3 fatty acids, arginine, and nucleotides—but no glutamine—sustained significantly fewer infections and wound complications than patients receiving an isonitrogenous diet.[16] A major shortcoming in other studies of IEDs is the consideration of total nitrogen load; arginine or glutamine were excluded from consideration because these amino acids were administered as pharmacologic nutrients. In these studies, patients received significantly more nitrogen as either protein or as amino acids in the IED. This increased nitrogen load may be clinically important; Alexander et al.[17] demonstrated that protein supplementation improved outcome in pediatric burn patients by reducing infectious complications and reducing length of stay per percent body burn.

This clinical trial evaluates severely injured trauma patients randomized to an enteral diet containing glutamine, arginine, nucleic acids, and omega-3 fatty acids (Immun-Aid, McGaw, Inc., Irvine, CA) or an isonitrogenous, isocaloric diet. Because our previous study[1] of enteral and parenteral nutrition noted that aggressive enteral nutrition was of benefit only in the most severely injured patients with an Abdominal Trauma Index (ATI) ≥ 25 or an Injury Severity Score (ISS) ≥ 21, the present investigation was limited to that patient population. Our goal was to determine whether an isonitrogenous diet could produce improved clinical outcome similar to that shown in a previous multi-institutional study of Immun-Aid in which our institution participated.[15] In addition, because of recent criticisms[18] that nutrition studies do not include a nonfed control population, we prospectively analyzed—without randomization—a third group. Because previous work[12] precluded randomization of severely injured patients to an unfed control for ethical reasons, we prospectively evaluated patients in whom enteral access had not been obtained by the operating surgeon but who otherwise met eligibility requirements for randomization. This allowed comparison of an IED and isonitrogenous enteral nutrition with contemporaneous controls who were not immediately fed but in whom nutrition support was instituted as clinically indicated. Outcome parameters included septic complications, duration of hospital stay, need for antibiotic therapy, and charges.

MATERIALS AND METHODS

Study Protocol

Fifty-four severely injured trauma patients requiring emergent celiotomy who were admitted to the Presley Memorial Trauma Center at The University of Tennessee, Memphis, between March 1994 and June 1995 comprised the study population. The study design and consent were approved by the Institutional Review Board of The University of Tennessee, Memphis. Thirty-five severely injured patients with an ATI ≥ 25 or an ISS ≥ 21 who had early enteral access obtained were randomized to the study diet (Immun-Aid; n = 17) or an isonitrogenous, isocaloric diet (ISO; n = 18). Patients eligible by severity of injury but without early enteral access at celiotomy served as contemporaneous controls (CONTROLS; n = 19) to evaluate outcome with no nutrition support. In the CONTROL group, the Nutrition Support Service instituted specialized nutrition only after consultation by the trauma service.

After management of intra-abdominal injuries, jejunostomy tubes were inserted distal to the ligament of Treitz using a 7-French needle catheter jejunostomy (Compat needle catheter jejunostomy kit, Sandoz Nutrition, Minneapolis, MN) or a standard red rubber catheter chosen at the discretion of six trauma service surgeons. Inclusion and exclusion criteria are noted in Table 1. Within 8 hours of operation, the nutrition support service at The Regional Medical Center at Memphis was consulted after informed consent was obtained. Patients were assigned by the Pharmacy Research Division to either the IED or isonitrogenous control diet using a computer-generated randomization table. Only one member of the nutrition support service was unblinded to study group to ensure correct randomization; this individual (TL) was not involved in the diagnosis of complications.

The experimental diet was compared with an isonitrogenous, isocaloric formula made up of four cans of Promote (Ross Laboratories, Columbus, OH) with an additional 22 g of protein (Casec, Mead-Johnson Nutrition-

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Address reprint requests to Kenneth A. Kudsk, M.D., Department of Surgery, The University of Tennessee, Memphis, 956 Court Avenue, Suite E228, Memphis, TN 38163.
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Table 1. INCLUSION/EXCLUSION CRITERIA FOR OUTCOME EVALUATION

Inclusion criteria
1) Age 18–65 years old
2) ISS ≥ 21
3) ATI ≥ 25
4) Glasgow Coma Scale ≥ 7
5) Candidate for enteral feeding

Exclusion criteria
1) Pregnancy (documented by serum or urine beta-HCG)
2) Any genetic immune or autoimmune disorder
3) Recipient of an organ transplant
4) Known insulin-dependent diabetes mellitus
5) Hepatic dysfunction defined as a serum total bilirubin >2.5 mg/dL or a known history of cirrhosis
6) History of chronic obstructive pulmonary disease
7) Prior positive test for HIV; no confirmatory testing for HIV antibody will be done
8) Confirmed sepsis or suspected to have an infection or sepsis at time of study entry
9) Metastatic cancer
10) Systemic steroids more than 48 hours
11) Immunosuppressive drugs, chemotherapy, or radiation therapy within the previous 6 months
12) Congestive heart failure or complicated cardiac disease
13) Existing renal disease defined as requiring chronic peritoneal dialysis, hemodialysis, or a serum creatinine >2.5 mg/dL
14) Head injury with a Glasgow Coma Scale score <7 at 24 hours postinjury
15) Mentally incompetent
16) Imprisoned individuals who do not have the ability to make a truly voluntary and uncoerced decision

ISS = Injury Severity Score; ATI = Abdominal Trauma Index; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus.

als, Evansville, IN) and 50 mL of water providing the nutrient composition and volume noted in Table 2. All postoperative management was directed by the operative surgeons responsible for the trauma intensive care unit (ICU). A rate providing 0.32 to 0.38 g of nitrogen/kg/day served as the nutrient goals for both groups. Experimental design allowed total parenteral nutrition (TPN) if the randomized patients were not receiving 66% of nutrient goal by 7 days, but no patients in these groups received TPN. There were no protocol violations in the randomized, prospective study.

Non-nutritional management of patients for both intra- and extra-abdominal injures remained standard for our institution throughout the study. Patients sustaining blunt or penetrating trauma were explored for signs of peritoneal irritation or hemodynamic instability and continued intra-abdominal bleeding. Computerized tomography was performed to evaluate the presence of blunt intra-abdominal injuries in hemodynamically stable patients. Solid-organ injuries were explored only if the patients had increasing blood requirements suggestive of continued intraperitoneal bleeding. When diagnostic peritoneal lavage was used, standard criteria (erythrocytes ≥ 100,000/mm^3, leukocytes > 500/mm^3) were used to assess abdominal injury. Patients with gunshot wounds that traversed the abdominal cavity underwent celiotomy. Perioperative broad-spectrum antibiotics were administered prophylactically to all patients for no more than 24 hours for intra-abdominal injury unless prophylactic antibiotics were dictated by specialty services. Skin and subcutaneous tissue were left open for delayed primary closure in the presence of fecal and significant gastric contamination. The time from surgery to institution of feeding was noted, and the rates of enteral feeding were advanced as tolerated by the clinical condition of the patients. Nasogastric decompression continued for at least 3 days. Nursing personnel flushed jejunostomy tubes with 10 mL of saline every 8 hours and administered no medications other than tube feedings through the jejunostomies. The ATI was calculated at the time of the initial jejunostomy placement or using the operative report. Nursing personnel of the trauma center registry calculated the ISS within 12 hours to provide an anatomic index of the severity of total body injury. Enteral nutrition continued until patients tolerated an oral diet.

Septic morbidity was defined as pneumonia, intra-abdominal abscess, empyema, or line sepsis during the first 15 days of entry. Clinical indications for pneumonia included the following: 1) abnormal temperature (>101 F or <96 F); 2) leukocytosis (leukocytes > 10,000 or >10% immature forms); 3) macroscopically purulent sputum; and 4) new or changing infiltrate on chest roentgenogram. Patients with clinical evidence of pneumonia then underwent fiberoptic bronchoscopy with bronchoalveolar lavage, as described previously.[19] Without using suction, the bronchoscope was advanced into the involved lung segment, as evidenced by chest roentgenogram results, or into the left lower lobe in cases of bilat-

Table 2. NUTRIENT COMPOSITION OF DIETS

	Promote with Casec®*	Immun-Aid®†
Volume	998 mL	1,000 mL
Nitrogen	13 g	13 g
CHO	123.2 g	120 g
Fat	24.6 g	22 g
% Fat	22%	20%
Total kcal	1040 kcal	1000
NPC kcal	714 kcal	680 kcal
NPC:N_2	55	52

CHO = carbohydrate; NPC = nonprotein calorie.
* Promote, Ross Laboratories, Columbus, OH; Casec, Mead-Johnson Nutritionals, Evansville, IN.
† Immun-Aid, McGaw, Inc., Irvine, CA.

eral diffuse infiltrates. With the tip of the bronchoscope wedged in the lower airway, bronchoalveolar lavage with 100 mL of sterile nonbacteriostatic saline was performed in 20-mL aliquots, and the effluent was pooled. The specimen was sent to the microbiology laboratory within 15 minutes for Gram's stain, quantitative bacterial culture (expressed as colony-forming units/mL), and sensitivities (bioMerieux Vitek, Inc., Hazelwood, MO). A portion of the sample was also analyzed for cell count and differential, presence of intracellular organisms, and evidence of viral effect. Pneumonia was diagnosed if quantitative cultures grew $\geq 10^5$ colony-forming units/mL; an exception was made for one ISO patient with 4×10^4 colony-forming units/mL who immediately defervesced with the institution of antibiotics effective against the organism cultured from that patient. Intra-abdominal abscess or empyema was defined as the presence of a purulent collection in the abdominal cavity or thoracic cavity requiring drainage by laparotomy, thoracostomy tube, or computed tomography-directed catheter placement. Necrotizing fascitis and wound infections associated with wound dehiscence were considered major septic complications. Minor wound infections and urinary tract infections were considered minor septic complications.

At the time of hospital discharge, all charts were reviewed by the principal investigator for confirmation of infection, the length of hospital stay, the number of ventilator days, the number of days receiving tube feedings, blood administration in the first 24 hours and during total hospitalization, and antibiotic usage. Antibiotics were classified into three categories. Prophylactic antibiotics were those that were administered after laparotomy for a viscus injury and were limited to 24 hours. In addition, prophylactic antibiotics were administered by orthopedic and other specialty services after bony, bony/soft tissue, or neurosurgical injuries. Empiric antibiotics were those administered for suspected infection but, with the return of culture data, proved to be unnecessary for management and were discontinued. Therapeutic antibiotics were those that may have been started empirically and were continued when definitive infection was diagnosed. The initial "empiric days" were reclassified as therapeutic days once the culture results had been obtained. The code for enteral diet type was broken only after diagnosis of septic complications and final entry of data into the computerized database.

Statistical Analysis

The data are expressed as means ± standard error of the mean. All discrete (categoric) variables were tested for statistical significance with Fisher's exact test or chi-square test of homogeneity, and all continuous variables were tested with Wilcoxon's rank sum test or median test. The significance testing and reported p values are two-sided for demographics and nutrition parameters, and one-sided for outcome, antibiotic usage, and hospital stay variables. All statistical analyses were performed using SAS system Version 6.11 under Microsoft Windows (SAS Institute Corp., Cary NC).

RESULTS

There was one death from progressive multiple-organ failure in each of the two enterally fed groups, which occurred within 5 days of admission, and data from these patients were excluded from further analysis. No significant differences in age, ISS, ATI, mechanism of injury, or Glasgow Coma Scale existed among the three groups (Table 3). Although there were minor differences in distribution of injuries among the three groups, only a few might be considered clinically significant. Duodenal injuries were significantly more common in the IED patients than CONTROL patients ($p = 0.04$), and this trend also was seen when compared with the ISO group ($p = 0.1$). The contemporaneous control group (CONTROL) had significantly more females than either of the two enterally fed groups. The CONTROL group had significantly more colon injuries than the ISO group ($p = 0.04$) with a similar trend ($p = 0.1$) when compared with the IED patients. Patients were classified by severity of colon injury into types 1 (contusion), 2 (less than 25% wall injury), 3 (25%–50% wall injury), 4 (75% wall injury), and 5 (a total destruction, requiring resection). Patients in the IED and CONTROL groups had more severe colon injuries than ISO patients (Table 4).

There were no significant differences in blood administration in ISO or IED patients, but the ISO group received a greater amount of blood during this total hospitalization and also within the first 24 hours. Close examination showed that the median amount of blood administered to the two groups was similar and most differences occurred in the seven ISO and six IED patients receiving >4000 mL of blood within the first 24 hours. The CONTROL patients received less blood than IED ($p = 0.05$) or ISO ($p = 0.07$) patients in the first 24 hours (Table 4) and had median blood administration significantly less than IED or IED patients ($p = 0.04$). After the first 24 hours, CONTROL patients appeared to require more blood than IED or ISO patients. However, this increase was secondary to two patients with courses complicated by upper gastrointestinal hemorrhage, multiple surgeries for intra-abdominal abscess or other complications, or prolonged ICU courses. These patients required 20,120 mL and 21,960 mL of blood, which accounted for 71% of blood administered to CONTROL patients after the first 24 hours. The remaining 17 CONTROL patients received 1144 ± 305 mL of blood after

Table 3. DEMOGRAPHICS AND DISTRIBUTION OF INJURED ORGANS

	Prospective. Randomized			Prospective		
	IED (16)	ISO (17)		Control (19)	*vs.* IED	*vs.* ISO
Deaths	1	1	NS	0	NS	NS
M/F	15/1	15/2	NS	10/9	p = 0.01	p = 0.03
Blunt	4/16 (25%)	7/17 (41%)	NS	4/19 (21%)	NS	NS
Age (yrs ± SEM)	34.3 ± 3.1	31.8 ± 2.3	NS	35.7 ± 2.8	NS	NS
ISS	25.1 ± 3.3	28.4 ± 2.9	NS	29.9 ± 2.7	NS	NS
Region injured						
Head/neck	1	4	NS	1	NS	NS
Chest	6	8	NS	9	NS	NS
Abdomen	15	17	NS	19	NS	NS
Extremities	6	6	NS	6	NS	NS
ATI	38.6 ± 4.3	30.7 ± 3.2	NS	32.6 ± 2.1	NS	NS
Colon	6	5	NS	13	p = 0.1	p = 0.4
Vascular	3	3	NS	3	NS	NS
Pancreas	4	3	NS	4	NS	NS
Duodenum	4	3	NS	0	p = 0.04	p = 0.10
Liver	7	10	NS	8	NS	NS
Spleen	7	5	NS	2	p = 0.05	NS
Stomach	4	4	NS	2	NS	NS
Small bowel	7	2	p = 0.06	8	NS	p = 0.07
Gallbladder	0	4	p = 0.10	3	NS	NS
Pelvis	3	4	NS	2	NS	NS
Diaphragm	5	5	NS	1	p = 0.07	p = 0.08
Kidney	7	4	NS	4	NS	NS
GCS	13.9 ± 0.6	13.8 ± 0.6	NS	13.7 ± 0.5	NS	NS

IED = immune-enhancing diet; ISO = isonitrogenous, isocaloric diet; NS = not significant; SEM = standard error of the mean; ISS = Injury Severity Score; ATI = Abdominal Trauma Index; GCS = Glasgow Coma Scale.

the first 24 hours, with a total blood loss of 3220 ± 964 mL, similar to the ISO and IED patients.

Feedings were started 1.63 ± 0.16 days and 1.97 ± 0.23 days after admission in the IED and ISO groups, respectively. The ISO patients remained on a diet slightly longer than the IED patients. Nitrogen and caloric intake/kg was the same in the two fed groups. There were no significant differences in albumin, prealbumin, transferrin, bilirubin, or leukocyte levels between randomized groups on either baseline or on day 7 (Table 5). Similarly, there were no significant differences in blood urea nitrogen, creatinine, glucose, triglyceride, magnesium, phosphorus, or potassium levels between the two groups (data not shown). Blood urea nitrogen levels increased significantly in both fed groups over the first week as a result of high nitrogen intake (IED: 11.6 to 21.4 mg/dL; ISO: 12.3 to 23.7 mg/dL).

The IED group had a significantly reduced number of septic complications compared with ISO or CONTROL patients (Table 6). The IED patients experienced significantly fewer intra-abdominal abscesses than other groups, with the highest incidence of abscess formation within the CONTROL group. No intra-abdominal abscesses developed in patients with colon injuries who were receiving the IED; this complication developed in approximately two thirds of the ISO and CONTROL patients. There was a strong trend toward increased incidence of pneumonia in the unfed CONTROL group compared with the IED group, barely missing statistical significance (p = 0.07). Bacteremia also was significantly lower in the IED group than the CONTROL group. Patients receiving the IED sustained significantly fewer total septic complications (minor or major) than CONTROL patients (p = 0.03), which also approached statistical significance *versus* the ISO group (p = 0.06). There were significantly fewer major septic complications—defined as the presence of pneumonia or abscess—in the group randomized to the IED compared with the ISO diet (p = 0.02) or unfed CONTROLS (p = 0.002). The number of septic complications per patient was significantly lower with IED than with either group, and patients randomized to IED, when infected, had significantly fewer infections than unfed CONTROL patients.

This reduction in septic outcome with the IED significantly impacted antibiotic usage and reduced hospital stay, and it reduced ICU stay (Table 7). Patients randomized to the IED received significantly fewer days of therapeutic antibiotics than patients randomized to the

Table 4. DEMOGRAPHICS—BLOOD LOSS AND COLON INJURIES

	Prospective Randomized			Prospective		
	IED (16)	ISO (17)		Control (19)	*vs.* IED	*vs.* ISO
Blood administered (mL)						
Total (±SEM)	3782 ± 682	5722 ± 1477	NS	5540 ± 1780	NS	NS
First 24 hours						
Average	3216 ± 594	4117 ± 1134	NS	2143 ± 743	p = 0.05	p = 0.07
Median	2725	2068	NS	800	p = 0.04	p = 0.04
None	2	3		6		
1-1000	1	1		5		
1001-2000	3	4		2		
2001-3000	3	2		0		
3001-4000	1	0		3		
>4000	6	7		3		
Severity of colon injury						
I	—	1		—		
II	1	4		2		
III	—	—		4		
IV	1	—		3		
V	4	—		4		

IED = immune-enhancing diet; ISO = isonitrogenous, isocaloric diet; SEM = standard error of the mean; NS = not significant.

ISO (p = 0.02) or CONTROL group (p = 0.002). Although not reaching statistical significance (p = 0.08), unfed CONTROL patients received more than twice as many days of therapeutic antibiotics as patients randomized to the ISO diet. Hospital stay was significantly reduced with the IED compared with ISO (p = 0.03) or control (p = 0.03) diets. Intensive care unit stay and ventilator days were highest in the unfed CONTROLS; patients randomized to the IED had the shortest ICU stay and ventilator days, with ISO patients midway between. These values failed to reach statistical significance because of the wide standard deviations. Hospital charges reflected this resource utilization with the highest charges in unfed controls and lowest charges in IED patients.

Table 5. NUTRITION PARAMETERS

	Prospective, Randomized		
	IED	ISO	
Days receiving diet (±SEM)	8.8 ± 1.5	10.2 ± 1.2	NS
Intake volume (mL)	1386 ± 116	1409 ± 80	NS
Initial weight (kg)	78.7 ± 3.7	86.8 ± 5.8	NS
Nitrogen intake (g/kg/day)	0.23 ± 0.02	0.23 ± 0.02	NS
Calorie intake (kcal/kg/day)	18.03 ± 1.62	18.29 ± 1.60	NS
Albumin (g/dL)			
Baseline	2.8 ± 0.1	2.7 ± 0.2	NS
Day 7	2.7 ± 0.2	2.8 ± 0.2	NS
Prealbumin (mg/dL)			
Baseline	14.4 ± 0.8	15.7 ± 1.0	NS
Day 7	12.9 ± 1.1	14.6 ± 1.2	NS
Transferrin (mg/dL)			
Baseline	173 ± 12	173 ± 6	NS
Day 7	221 ± 13	207 ± 16	NS
Bilirubin (mg/dL)			
Baseline	0.7 ± 0.3	0.8 ± 0.2	NS
Day 7	1.5 ± 0.4	2.6 ± 1.0	NS
Leukocyte count × $10^3/mm^3$			
Baseline	12.1 ± 1.4	11.6 ± 1.6	NS
Day 7	16.8 ± 2.3	21.0 ± 2.5	NS

IED = immune-enhancing diet; ISO = isonitrogenous, isocaloric diet; SEM = standard error of the mean; NS = not significant.

Thirteen of 16 IED patients developed gastrointestinal side effects, such as abdominal distention, diarrhea, and cramps *versus* 16 of 17 ISO patients. Gastrointestinal side effects necessitated slowing the formula administration in 50% of patients receiving Immun-Aid and 41% of patients receiving the control diet at some point during recovery. These values were not significantly different in the two groups. Of the 19 patients in the unfed CONTROL group, only 2 patients received nutrition before the diagnosis of infection. One patient received a single day of gastric feeding at 25 mL/hour and a second received 3 days of TPN and 2 days of gastric feeding before the diagnosis of pneumonia and bacteremia. The remaining patients received intravenous dextrose solutions only and no specialized nutrition support before the development of infectious complications.

DISCUSSION

In a changing health-care environment, outcome parameters are receiving increasing attention from insur-

Table 6. OUTCOME: SEPTIC COMPLICATIONS

	Prospective, Randomized			Prospective		
	IED (16)	ISO (17)		Control (19)	*vs.* IED	*vs.* ISO
Intra-abdominal abscess	1 (6%)	6 (35%)	p = 0.05	9 (47%)	p = 0.009	NS
IAA with colon injury	0/6	3/5 (60%)	p = 0.06	6/13 (46%)	p = 0.06	NS
Pneumonia	0	2 (12%)	NS	4 (21%)	p = 0.07	NS
Bacteremia	1 (6%)	4 (24%)	NS	8 (42%)	p = 0.02	NS
Wound infection						
Major	1 (6%)	0	NS	3 (16%)	NS	NS
Minor	1 (6%)	3 (18%)	NS	1 (5%)	NS	NS
UTI	2 (13%)	6 (35%)	NS	4 (21%)	NS	NS
Sepsis syndrome	0	2 (12%)	NS	0	NS	NS
Patients with any septic complications	5 (31%)	11 (65%)	p = 0.06	13 (68%)	p = 0.03	NS
Patients with major septic complications (IAA and/or pneumonia)	1 (6%)	7 (41%)	p = 0.02	11 (58%)	p = 0.002	NS
No. of septic complications per patient (±SEM)	0.38 ± 0.15	1.41 ± 0.36	p = 0.01	1.58 ± 0.32	p = 0.003	NS
No. of septic complications per infected patient	1.2 ± 0.2	2.2 ± 0.4	p = 0.09	2.3 ± 0.3	p = 0.03	NS

IED = immune-enhancing diet; ISO = isonitrogenous, isocaloric diet; NS = not significant; IAA = intra-abdominal abscess; UTI = urinary tract infection; SEM = standard error of the mean.

ance companies, managed health-care organizations, and hospital administrators, as well as individual practicing physicians. For any therapeutic intervention, outcome measures include not only reduction of morbidity and mortality, but also reduction of resource utilization and cost. Although a significant body of data justifies feeding via the gastrointestinal tract rather than intravenously,[1-4] two additional issues confront the clinician. First, is one type of enteral nutrition significantly better than another, and second, is specialized nutrition support justified within the short term of 1 to 2 weeks after injury or illness? This randomized, prospective study documents that a specialized enteral formula significantly reduces septic complications while reducing charges compared with isonitrogenous standard diets. Use of the specialized diet also significantly improves outcome compared with patients receiving minimal, if any, early nutrition intervention.

Our previous study[1] of 98 severely injured trauma patients who were randomized to enteral and parenteral feeding confirmed earlier work[2,3] by the Denver group that enteral feeding significantly reduces major septic complications, such as intra-abdominal abscess and pneumonia, compared with patients fed intravenously.

Table 7. ANTIBIOTIC USAGE AND HOSPITAL STAY

	Prospective, Randomized			Prospective		
	IED (16)	ISO (17)		Control (19)	*vs.* IED	*vs.* ISO
Antibiotic use (days ± SEM)						
Prophylactic	3.8 ± .9	2.7 ± .5	NS	4.2 ± .7	NS	NS
Empiric	1.4 ± .8	2.6 ± 1.1	NS	0.7 ± .5	NS	NS
Therapeutic	2.8 ± 1.6	7.1 ± 1.7	p = 0.02	17.4 ± 4.6	p = 0.002	p = 0.08
Hospital stay (days ± SEM)						
Total	18.3 ± 2.8	32.6 ± 6.6	p = 0.03	34.9 ± 6.0	p = 0.03	NS
In ICU	5.8 ± 1.8	9.5 ± 2.3	p = 0.10	15.7 ± 4.9	NS	NS
On ventilator	2.4 ± 1.3	5.4 ± 2.0	p = 0.09	9.0 ± 4.2	NS	NS
Hospital charges	$80,515 ± 21,528	$110,599 ± 19,132	p = 0.10	$141,049 ± 34,396	NS	NS

IED = immune-enhancing diet; ISO = isonitrogenous, isocaloric diet; SEM = standard error of the mean; NS = not significant; ICU = intensive care unit.

The 1986 Denver study[2] also demonstrated a significant benefit of instituting early enteral feeding compared with no early feeding. Our initial study[1] showed that patients with low ATI (<25) or low ISS (<21) did not benefit from enteral feeding. Septic complications were low, and we concluded that nutrition probably was not an important factor in the postinjury recovery of these two groups. Most of the benefit occurred in patients with an ATI ≥ 25, an ISS ≥ 21, or in patients with both high ISS and ATI in whom the risk of septic complications increased with intravenous TPN by 6.3, 7.3, and 11.3 times, respectively. The current study focuses on that subpopulation to test the nutrient formulas. Because the first Denver study[2] showed increases in septic complications when no specialized nutrition was given in the first 5 days after injury, we believed that it was unethical to randomize patients to an unfed CONTROL group and limited the prospective randomization to either the IED or to an isonitrogenous, isocaloric diet. Because our standard practice does not include intravenous nutrition in the early postinjury phase in otherwise well-nourished trauma patients unless complications develop or it becomes clear that the patient will not take an adequate oral diet or tolerate intragastric tube feedings, we felt no moral obligation to immediately begin intravenous TPN in our contemporaneous CONTROL group. We believe the increase in septic complications with intravenous TPN noted in our first study,[1] as well as in the Veterans Affairs Cooperative Study[20] of general surgery patients, and the study by Brennan[21] of postoperative TPN after pancreatic resection, justify this approach. Although not randomized to this group, the unfed population serves as a reasonable benchmark for the risk of septic complications in patients with high ISS and ATI.

In the prospective, randomized portion of our study, patients received a commercial diet enriched with glutamine, arginine, nucleotides, and omega-3 fatty acids (Immun-Aid) or an isonitrogenous, isocaloric control diet. During the past several decades, the specialty nutrients in the IED have demonstrated benefit in studies of sepsis, immunity, altered intestinal permeability, and inflammation.[22–37] Over the last 10 years, several randomized, prospective published studies comparing diets containing some or all of these specific nutrients have shown positive clinical benefits, including reduced septic complications, shorter hospital stay, and improved outcome.[10–16] Unfortunately, all but two[11,16] have compared an IED against control diets that were not isonitrogenous. The rationale for this approach was that because the specific amino acids, arginine or glutamine, were being administered as pharmacologic agents, the nitrogen contribution from these amino acids should be ignored in the comparison studies. Although there is some logic to this approach, these studies have generated criticism since Alexander et al.[17] demonstrated that septic morbidity and length of stay per percent body burn were significantly reduced in burned pediatric patients randomized to a protein-supplemented diet in 1980. Because of this confounding variable, results of IED studies using nonisonitrogenous control diets were viewed suspect because there was only one study[16] comparing an immune-enhancing formula with an isonitrogenous control in which significant improvement was noted.

To unravel this confounding variable, our study randomized patients with a high risk of septic complications to either the IED or an isonitrogenous, isocaloric control. Overall, the average ATI in the 52 patients was 33.8 ± 1.9 with an intra-abdominal sepsis rate of 30.7% (16 of 52 patients), a sepsis rate nearly identical to our previously published results correlating the ATI with abdominal septic complications.[38] However, although that initial work failed to consider route or type of nutrition, the present study confirms earlier work that delayed enteral feeding increases the risk of septic complications.[2] Our major sepsis rate of 41% in the isonitrogenous control patients was higher than the severely injured supplementation in our enteral/parenteral study, but most of this increase is accounted for by restricting inclusion to patients with high ISS and ATI scores. In the severely injured enterally fed subpopulation in our initial study, 5 of the 11 patients had an ISS < 20 and 3 of 11 patients had an ATI < 24. In addition, patients in the ISO and IED groups had a higher incidence of liver, duodenal, and splenic injuries than in our previous study.

The ISO and IED groups were well matched, with similar magnitude and distribution of injuries. Both groups received identical nitrogen and caloric intake/kg/day and received the diet for approximately the same duration. Despite similar success in feeding the groups during the experiment, there were significantly fewer intra-abdominal abscesses and major septic complications in patients receiving the supplemented diet compared with a standard isonitrogenous enteral diet. This improved outcome was reflected in a significant reduction in therapeutic antibiotic usage. Total hospital days were significantly reduced with the IED, and although the numbers did not reach statistical significance, ICU stays were decreased by 40% and ventilator days were reduced by 55% with the IED diet compared with the isonitrogenous diet. This translated into a reduction in hospital charges as well; however, this did not reach statistical significance because of the range of distribution. From these data, we recommend using an IED in critically injured patients at high risk of developing septic complications as soon as it is clinically safe after surgery and continuing until the risk of septic complications is low. Because of the benefit documented by Bower in this subgroup,[10] we recommend continuing these diets in patients in whom infectious complications develop.

The study formula contained several specialty nutri-

ents used in IED, and it is unclear which particular nutrient or combination of nutrients improved clinical outcome. Although one clinical study showed that a diet modified only by omega-3 concentration (fish oil in that particular study) produced changes in biochemical parameters and an improvement in infectious complications, significantly greater use of TPN in the patients receiving the non-fish oil-supplemented diet presented a major confounding variable.[39] Although some have warned that the IEDs might aggravate the inflammatory response after injury, the preponderance of data would not suggest that this is a significant problem.

Although not randomized, the contemporaneous CONTROL group serves a very important function that should not be ignored. This group was prospectively included to study the merit of criticisms raised within the nutrition literature.[8] This author argues that because most clinical studies fail to include an unfed population and because of the potential for treatment complications, early specialized nutrition support may be unnecessary and perhaps harmful, suggesting that nutrition support be withheld for up to 2 weeks. Because the first Denver study[2] clearly showed a higher incidence of septic complications in unfed patients compared with those in the early enterally fed group, we could not ethically justify randomization to this treatment arm. However, over the course of the study, 19 patients admitted to our trauma ICU met entry criteria but had no enteral access, precluding early postligament of Treitz feeding.

The ISS and ATI of this contemporaneous control group were not significantly different from the other two groups, but there were more women and more colon injuries in this group. It was not always clear why these patients were not cannulated. In some circumstances, the operating surgeon believed that a patient had a low risk of sepsis because blood loss was minimal, but the outcome proved this assumption wrong. As a group, the CONTROL patients did require less blood in the acute situation. In some situations, ATI's were underestimated; *e.g.,* in one case, a spinal cord injury secondary to a gunshot wound initially was unrecognized and not included when calculating the ATI. At other times, enteral access was overlooked at the completion of the procedure. In general, failure to gain access was not associated with an individual surgeon, and episodes occurred at random throughout the study.

Because the patients would otherwise have been included in this study, they were considered appropriate to document the risk of septic complications in patients with high ISS or ATI, despite no formal randomization. Colon injuries were more frequent in this group, but patients receiving the IED had nearly as many severe colon injuries (grades 4 and 5) as the unfed group. Although major colon injury predicts a high rate of intra-abdominal abscess,[40] this complication did not develop in any of the six patients receiving the IED, whereas abscesses formed in almost 50% of unfed patients, barely missing statistical significance ($p = 0.06$). The incidence of intra-abdominal abscesses in the patients receiving the isonitrogenous diets was about the same as the control diet, despite the fact that the colon injuries were less severe in this group; this suggests that colon injuries *per se* are not always the source of sepsis or that severity of contamination may be more important. The unfed controls consistently had the highest rate of intra-abdominal abscess, pneumonia, bacteremia, major septic complications, and number of septic complications per patient. These reached statistical significance compared with the IED, but did not reach statistical significance compared with the isonitrogenous controls, although the isonitrogenous control population always had a lower rate of complications. Unfed controls received similar courses of prophylactic and empiric antibiotics but received more days of therapeutic antibiotics than the isonitrogenous control subjects and significantly more than the patients receiving the IEDs. Length of hospital stay, ICU stay, and ventilatory days paralleled these results. As expected, average hospital costs were highest in the unfed control although this did not reach statistical significance when compared against either fed group. Although it did not reach statistical significance, the lowest incidence of pneumonia occurred in groups that were enterally fed, barely missing statistical significance between IED and the unfed patients. These data are consistent with our experimental observation that enteral feeding maintains upper respiratory tract immunity.[6]

This prospective study demonstrates that in severely injured patients, fasting does not produce results that are comparable to those in patients receiving specialized enteral nutrition support. Hospital stay, infectious complications, hospital costs, and antibiotic usage were highest in the unfed group. Our study confirms other published studies of the clinical benefits of an IED compared with other more "standard" enteral diets. Although the beneficial component or components that generate this improved benefit may never be identified definitively, these specialized diets reduce septic morbidity and hospital costs and should be considered the most beneficial form of enteral specialized nutrition support in the immediate postoperative phase after severe blunt and penetrating trauma—and perhaps other critically ill patient populations at risk of sepsis.

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Discussion

DR. MARTIN ALLGOWER (Pratteln, Switzerland): I think this beautiful demonstration has reminded us of the landmark pa-